REMARKS

I. Status of the Claims

Claims 1-20, 25-27, 29-40 and 43-57 are pending in the application. Claims 29, 30, 43, 44 and 46-49 are withdrawn and claims 21-24, 28, 41 and 42 were previously cancelled. Claims 1-20, 25-27, 31-40, 45 and 50-57 are rejected.

II. Novelty Rejection

The Office maintains the prior rejection of claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 under 35 U.S.C. § 102(e) as allegedly anticipated by Cummings et al., U.S. Patent No. 5,464,778 ("Cummings"), as further evidenced by The Merck Manual of Diagnosis and Therapy (17th ed.) ("Merck Manual"). Cummings allegedly teaches treatment of (1) stroke; (2) atherosclerosis; and (3) ischemia/reperfusion injury. The Office states that the cited passages from the Merck Manual "provide evidence that the prior art targeted conditions and diseases were associated with hypertension." Office Action, p. 3.

A. The Office Fails To Rely On The Proper Legal Standard For Determining Inherency, Which Requires That The Missing Descriptive Matter Is Necessarily Present In The Applied References

In rejecting claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 for alleged anticipation, the Office contends that, despite the fact that the "prior art targeted patient populations do not necessarily have or develop hypertension, *one of ordinary skill in the art would have immediately envisaged at the time the invention was made* that the prior art treatment of ischemia-reperfusion injury, atherosclerosis, and strokes was targeting patients with hypertension." *Id.* (emphasis added). This is not the proper standard for determining inherency.

A claim is anticipated "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP § 2131 (8th ed., 2d rev. 2004) (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987)). Normally, only a single reference should be used in rejecting an application under 35 U.S.C. § 102, though a § 102 rejection over multiple references has been found proper where the additional reference was cited: (1) to prove the primary reference contains an enabled disclosure; (2) to explain the meaning of a term used in the primary reference; or (3) to show that a characteristic not disclosed in the primary reference is inherent. MPEP § 2131.01. The reference "must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill." MPEP § 2112 (citing *Schering Corp. v. Geneva Pharmaceuticals, Inc.*, 339 F.3d 1373, 1376 (Fed. Cir. 2003)) (emphasis added). Finally, inherency "may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." MPEP § 2112 (citing *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)). The burden is on the Office to "provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 (citing *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990)). The Applicants respectfully submit that the Office has failed to meet this initial burden, because it has not demonstrated that hypertension is necessarily present in the conditions of Cummings.

B. Hypertension is Not Necessarily Associated with the Conditions of Cummings

In rejecting claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57, the Office fails to meet its burden in showing that hypertension is necessarily associated with the conditions of Cummings. The Office cites to The Merck Manual to show that hypertension is inherent in the conditions of Cummings. Office Action, p. 3. However, the Merck Manual exemplifies the distinct nature of hypertension and the conditions of Cummings. For example, the Merck Manual describes the characteristics of atherosclerotic vessels and then describes the distinct characteristics of such vessels when hypertension is present. THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1655 (17th ed. 1999). This description indicates that hypertension and atherosclerosis need not coexist. In fact, hypertension is not listed as a symptom characteristic of atherosclerosis in the passage of the Merck Manual cited by the Office, which states that "[a]therosclerosis is characteristically silent until critical stenosis, thrombosis, aneurysm, or embolus supervenes." THE MERCK MANUAL OF DIAGNOSIS AND THERAPY 1657 (17th ed. 1999). Moreover, the Office cites passages of the Merck Manual that describe hypertension as a "risk factor" for several diseases. Office Action, p. 3. For example, the Office quotes the Merck Manual's statement that hypertension is one of "three risk factors, along with cigarette smoking and hypercholesterolemia predisposing to coronary atherosclerosis" and hypertension is the "most important risk factor predisposing to stroke." *Id.* The Merck Manual's treatment of these "risk factors" highlights how these may alter the probability or possibility of a particular disease but are not necessarily associated with the disease. The fact that some risk factors are

more "important" than others may suggest a stronger association, but not that the risk factor and the disease are necessarily associated. For instance, atherosclerosis can be caused by hypercholesterolemia, and a stroke may be caused by an embolism, as applicants have previously argued. In these instances, hypertension would not necessarily be associated with the conditions of Cummings.

C. It Is Known To Those Of Skill In The Art That Hypertension Is Not Necessarily Present In The Conditions Of Cummings

The Merck Manual merely indicates that there may be a correlation between hypertension and various conditions, but hypertension is just one of many risk factors that might predispose to certain conditions. It is well known by those skilled in the art that patients with atherosclerosis need not also have hypertension. See Hemmerich Declaration, paragraph 7(A) ("Declaration").

The Merck Manual teaches that strokes can be caused by arteriosclerotic or hypertensive stenosis, thrombosis or embolism. (See page 1421). The Merck Manual does not teach that stroke is necessarily associated with hypertension. In totality, the Merck Manual indicates that hypertension and stroke do not always coexist and patients suffering from a stroke do not always have hypertension. This is well known among those skilled in the art. See Declaration, paragraph 7(B).

The Merck Manual teaches that a number of factors including hypertension predispose a patient to Transient Ischemic Attacks (TIA). However, it is known to those of skill in the art that ischemia and hypertension need not always coexist. See Declaration, paragraph 7(C).

The office has not met its burden for a showing of inherent anticipation because neither Cummings nor the Merck Manual show that hypertension is necessarily present in the diseases in Cummings, those of skill in the art recognize that hypertension is not necessarily present in the diseases in Cummings. Applicants respectfully request that the rejection of claims 1-4, 8-13, 16-18, 25-27, 45-47, 50-53, and 57 be withdrawn. Hypertension is not necessarily associated with atherosclerosis, strokes and injuries from ischemia and reperfusion, and one of ordinary skill in the art at the time the invention was made would not know whether a subject suffering from these conditions was also hypertensive. Accordingly, one of skill in the art at the time the invention was made could not envision that the treatments disclosed in Cummings were targeting patients with hypertension and the instantly claimed invention is not inherently anticipated.

III. Obviousness Rejections

The Office maintains the prior rejection of claims 1-20, 25-27, 31-40, 45, and 50-57 under 35 U.S.C.§ 103(a) as allegedly unpatentable over Cummings and Larsen *et al.*, U.S. Patent No. 5,840,679 ("Larsen") in view of Blann *et al.*, "Evidence of platelet activation in hypertension," *J. Hum. Hyper.* 11:607-609 (1997) ("Blann"), Araneo *et al.*, U.S. Patent No. 6,150,348 ("Araneo") and DeFrees *et al.*, U.S. Patent No. 5,604,207 ("DeFrees"), and further in view of the Merck Manual. Office Action, p. 5. The Office apparently contends that administration of PSGL-1 to treat the conditions recited in Cummings and Larsen would inherently treat hypertension, and therefore thrombosis.

A proper *prima facie* obviousness rejection requires some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Additionally, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. *See* M.P.E.P. § 2143. The Examiner bears the burden of establishing *prima facie* obviousness. *See* M.P.E.P. § 2142.

The Office continues to rely upon an improper finding of inherency, and thus motivation to combine references is lacking. Cummings and Larsen neither teach nor suggest the use of a PSGL-1 protein for treating or inhibiting thrombosis in a patient with hypertension. As noted above, Cummings neither teaches nor suggests that hypertension is necessarily associated with any of the conditions discussed therein, and the lack of necessary association between hypertension and the conditions of Cummings was known to those of skill in the art. See Declaration, paragraph 8. Larson, Blann, Araneo, Defrees and The Merck Manual also fail to show such a necessary association and do not provide the motivation to arrive at the claimed invention.

A. Larsen

Larsen describes a P-selectin ligand protein, and methods of treating numerous conditions using P-selectin ligand (See column 15, lines 50-66). Larsen does not mention treatment of subjects with hypertension and does not mention treatment of thrombosis. Larsen does not teach that conditions that might be treated with P-selectin ligand are associated with hypertension and does not teach that a composition having

P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. The disclosure in Larsen would not suggest to the skilled artisan that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. See Declaration, paragraph 10.

B. Blann

Blann merely speculates that compounds that reduce platelet activity, such as aspirin, could be useful to treat thrombosis but does not teach that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation, or deep vein thrombosis in a subject having hypertension. (See page 608). To one skilled in the art, the disclosure in Blann would not suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. See Declaration, paragraph 11.

C. Araneo

Araneo discusses methods of preventing or reducing effects of ischemia and other conditions including pulmonary hypertension by administering the steroid DHEA, a very different compound from the instantly claimed protein. (See Abstract. Also see column 4). Araneo does not teach or suggest that a composition having P-selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation, or deep vein thrombosis in a subject having hypertension, but suggests a treatment based on reducing the level of P-selectin expression. (See column 17, lines 59-64). To one skilled in the art, the disclosure in Blann would not suggest that a composition having P-

selectin ligand activity could be used to treat or inhibit thrombosis, thrombus formation or deep vein thrombosis in a subject having hypertension. See Declaration, paragraph 12.

D. DeFrees

DeFrees describes analogs of sialyl Le^X and speculates on the use of these compounds to treat inflammatory disorders, and mentions the use of these analogs to treat deep vein thrombosis. (See column 3 and column 44, lines 35-65. Also See column 45, lines 7-15). However, DeFrees does not teach or suggest the treatment of deep vein thrombosis in a subject with hypertension and fails to suggest any relationship between P-selectin or PSGL-1 and the treatment of thrombosis in a subject with hypertension. See Declaration, paragraph 13.

E. The Merck Manual

As noted above, The Merck Manual merely indicates that there may be a correlation between hypertension and certain conditions, but hypertension is just one of many risk factors that might predispose to these conditions. Moreover, it is well known by the skilled artisan that patients with thrombotic conditions need not also have hypertension. See Declaration, paragraphs 7-8.

Because of the shortcomings of Blann, Araneo, DeFrees and the Merck Manual, these publications fail to cure the deficiencies of Cummings and Larsen. First, none of these references teach or suggest that hypertension is necessarily associated with the conditions discussed in Cummings and/or Larsen. Second, each of Blann (the acetylcholinesterase inhibitor quinapril), Araneo (a dehydroepiandrosterone derivative), and DeFrees (analogues of sialyl-Lewis^X) discuss compounds other than a PSGL-1

protein for treating conditions other than thrombosis in a subject having hypertension. In the absence of a known or inherent association between hypertension and the conditions of Cummings or Larsen, one of skill in the art would have no motivation to arrive at the claimed invention by combining references. Accordingly, Applicants respectfully request that the rejection of claims 1-20, 25-27, 31-40, 45, and 50-57 be withdrawn.

IV. Rejection of Claim 27

The Office maintains the prior rejection of claim 27 under 35 U.S.C.§ 103(a) as allegedly unpatentable over Cummings and Larsen, in view of Blann, Araneo, DeFrees, the Merck Manual, as applied to claims 1-20, 25-27, 31-40, 45, and 50-57 above, and further in view of Maugeri *et al.*, "Polymorphonuclear Leukocyte-Platelet Interaction: Role of P-selectin in Thromboxane B_2 and Leukotriene C_4 Cooperative Synthesis," *Thromb. Haem.* 72:450-456 (1994) ("Maugeri") and Johnston *et al.,* "Differential Roles of Selectins and the α4-Integrin in Acute, Subacute, and Chronic Leukocyte Recruitment In Vivo," *J. Immunol.* 159:4514-4523 (1997) ("Johnston").

Claim 27 is directed to a method for inhibiting thrombus formation induced by leukotriene C_4 ("LTC_4") in a subject by identifying a subject at risk of thrombosis resulting from hypertension and administering to the subject a composition comprising an effective amount of soluble PSGL-1 protein or a fragment thereof. The Office conceded that Cummings and Larsen do not disclose the role of LTC_4 in thrombus formation or thrombotic conditions *per se*, but maintains that LTC_4 was a known thrombus-inducing agent involved in thrombus formation and thrombotic conditions, as allegedly shown by Maugeri and Johnston. Office Action, p. 8.

A. Maugeri

Maugeri investigates a relationship between LTC_4 and the aggregation of mixtures containing platelets and polymorphonuclear leukocytes, and describes decreased aggregation of these mixtures in the presence of an anti-P-selectin antibody *in vitro*. (See Introduction and Figure 2). Maugeri does not mention the use of a P-selectin ligand protein to treat thrombosis, and does not mention any relationship between thrombosis formation and hypertension. To one of ordinary skill in the art, the disclosure of Maurgeri would not suggest a method of treating or inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering to the subject a composition of a PSGL-1 protein, or said method wherein the thrombus inducing agent is LTC_4. See Declaration, paragraph 15.

B. Johnson

Johnston investigates the ability of anti-P-selectin antibodies to inhibit LTC4-induced leukocyte rolling in vitro (See e.g. Figure 1). Johnston speculates about anti-inflammatory strategies designed to block leukocyte recruitment but does not identify the use of a P-selectin protein. (See page 4532). Moreover, Johnston fails to teach or suggest any relationship between thrombus formation and hypertension. To one of ordinary skill in the art, the disclosure of Johnston would not suggest a method of treating or inhibiting thrombus formation induced by a thrombus-inducing agent in a subject comprising identifying a subject having hypertension and administering to the subject a composition of a PSGL-1 protein, or said method wherein the thrombus inducing agent is LTC4. See Declaration, paragraph 16.

As noted above, neither Larsen nor Cummings teach or suggest treating or inhibiting thrombosis in a subject with hypertension and Blann, Araneo, DeFrees or the Merck Manual do not compensate for this deficiency, since none of these documents discuss administering a PSGL-1 protein for treating or inhibiting thrombosis in a subject having hypertension. Similarly, neither Maugeri nor Johnston compensate for these deficiencies because they also fail to discuss treating or preventing thrombosis in a subject having hypertension using a P-selectin ligand protein. To one of skill in the art, Maugeri and Johnston would not render the claimed invention obvious. See Declaration, paragraph 17.

Accordingly, Applicants respectfully request the withdrawal of the rejection of claim 27.

V. Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration and reexamination of the application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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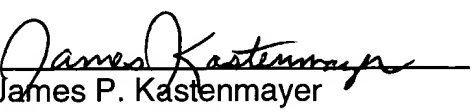
By: 
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